TFAP2C- and p63-Dependent Networks Sequentially Rearrange Chromatin Landscapes to Drive Human Epidermal Lineage Commitment.

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Authors: Lingjie Li, Yong Wang, Jessica L Torkelson, Gautam Shankar, Jillian M Pattison, Hanson H Zhen, Fengqin Fang, Zhana Duren, Jingxue Xin, Sadhana Gaddam, Sandra P Melo, Samantha N Piekos, Jiang Li, Eric J Liaw, Lang Chen, Rui Li, Marius Wernig, Wing H Wong, Howard Y Chang, Anthony E Oro

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Public Summary:
Tissue development results from lineage-specific transcription factors (TFs) programming a dynamic chromatin landscape through progressive cell fate transitions. Here, we define epigenomic landscape during epidermal differentiation of human pluripotent stem cells (PSCs) and create inference networks that integrate gene expression, chromatin accessibility, and TF binding to define regulatory mechanisms during keratinocyte specification. We found two critical chromatin networks during surface ectoderm initiation and keratinocyte maturation, which are driven by TFAP2C and p63, respectively. Consistently, TFAP2C, but not p63, is sufficient to initiate surface ectoderm differentiation, and TFAP2C-initiated progenitor cells are capable of maturing into functional keratinocytes. Mechanistically, TFAP2C primes the surface ectoderm chromatin landscape and induces p63 expression and binding sites, thus allowing maturation factor p63 to positively autoregulate its own expression and close a subset of the TFAP2C-initiated surface ectoderm program. Our work provides a general framework to infer TF networks controlling chromatin transitions that will facilitate future regenerative medicine advances.

Scientific Abstract:
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